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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/588,570	05/04/2007	Nicolas Zackes Rudinger	630196.401USPC	7112

500 7590 09/14/2010

SEED INTELLECTUAL PROPERTY LAW GROUP PLLC
701 FIFTH AVE
SUITE 5400
SEATTLE, WA 98104

EXAMINER	
HUTSON, RICHARD G	

ART UNIT	PAPER NUMBER
1652	

MAIL DATE	DELIVERY MODE
09/14/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/588,570	RUDINGER ET AL.	
	Examiner	Art Unit	
	Richard G. Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/6/2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6-9 and 14-34* is/are pending in the application.

4a) Of the above claim(s) *6-9 and 28-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,14-27,33 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment of claim 1, 9, 20, 23, in the paper of 7/6/2010, is acknowledged. Claims 1-2, 6-9, 14-34 are still at issue and are present for examination.

Applicants' arguments filed on 7/6/2010, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claims 6-9 and 28-32 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Information Disclosure Statement

Applicants comments that "Applicants are unclear about to which listing of references in the specification is objected and respectfully request that the Examiner clarify this objection." in response to the previous comments regarding references in the specification is acknowledged. No listing of references in the specification were objected to. The previous comments regarding an information disclosure statement were merely to remind applicants that just because applicants list or recite a reference in the specification is not a guarantee that those references will be considered in the patentability of the claims and only those references that are listed as part of a proper information disclosure statement are guaranteed to be so considered.

Specification

The disclosure is objected to because of the following informalities: Applicants specification on page 14, paragraph 6, recites the amino acid sequence "DYSQIELR" which requires a sequence identifier..

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The rejection of claim 1 (2, 14-27, 33 and 34 dependent on) based upon indefiniteness in the recitation "… at least the amino acid residue Q879 has been replaced by a lipophilic amino acid residue." is hereby withdrawn based upon applicant's amendment of the claims in the paper of 7/6/2010.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 14-27, 33 and 34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection was stated in the previous office action as it applied to previous claims 1. In response to this rejection applicants have amended claims 1, 9, 20, 23 and traverse the rejection as it applies to the newly amended claims.

Applicants submit that Claim 1 of the present application is directed to a family A DNA polymerase or its Klenow fragment that has a modified motif C sequence and enhanced mismatch discrimination as compared to the corresponding wild type polymerase or its Klenow fragment. Applicants submit that the term "family A DNA polymerase" is defined in the present application as referring to DNA polymerizing enzymes that contain the A motif with the sequence DYSQIELR in their active site. Thus, the family A DNA polymerase or its Klenow fragment according to claim 1 of the present application has the following two structural features: (1) it has the A motif with the sequence DYSQIELR in its active site, and (2) it has a modified motif C sequence in which at least the amino acid residue Q879 in the wild type motif C sequence QVH in positions 879-881 of the *E. coli* DNA polymerase Klenow fragment has been replaced by a lipophilic amino acid residue. Applicants submit that in addition, the family A DNA polymerase or its Klenow fragment claimed in the present application has the following two functional features: (1) it has DNA polymerase activity, and (2) it has an enhanced mismatch discrimination as compared to the corresponding wild type polymerase or its Klenow fragment.

Applicants disagree with the assertion in the Office Action that the claims are not limited structurally in any way. As indicated above, because the present application defines the term "family A DNA polymerase" as referring to a DNA polymerase that

contain the A motif with the sequence DYSQIELR in its active site, the claimed family A DNA polymerase or its Klenow fragment has motif A with the sequence DYSQIELR in its active site. Applicants submit that family A DNA polymerases and its Klenow fragments were well known and characterized in the art at the filing of the present application. More specifically, as indicated in Patel *et al.* (J. Mol. Biol. 308:823-837, 2001, "Patel," copy enclosed), over 50 family A polymerases from different prokaryotic species had been sequenced *(see,* Abstract). These studies in combination with mutagenesis analyses illustrated the structure-function relationship of family A DNA polymerases, including the function of individual amino acid residues in polymerization *(see,* pages 832-834).

Applicants submit that second, one of ordinary skill in the art would not doubt that the present inventors had possession of a family A DNA polymerase with an enhanced mismatch discrimination as compared to the corresponding wild type polymerase. As discussed above, the claimed DNA polymerase or its Klenow fragment has an additional structural feature: It has a modified motif C sequence in which at least the amino acid residue Q879 in the wild type motif C sequence QVH in positions 879-881 of the *E. coli* DNA polymerase Klenow fragment has been replaced by a lipophilic amino acid residue. The present application provides numerous exemplary substitutions of the QVH sequence *(see,* the third full paragraph on page 11). It further shows that certain exemplary substitutions of the QVH sequence resulted in enhanced mismatch discrimination activity of the modified DNA polymerases *(see,* Examples 3, 5 and 6, Figures 1-4).

In view of such disclosure provided by the present application, Applicants submit that one of ordinary skill in the art would not doubt the possession of a family A DNA polymerase with an enhanced mismatch discrimination as compared to the corresponding wild type polymerase by the present inventors.

Applicant's amendment of the claims and applicants complete argument is acknowledged and has been carefully considered, however, is not found persuasive for the reasons previously stated and for those reasons repeated herein.

It continues that applicants claims are drawn to any family A DNA polymerase or its Klenow fragment having a modified motif C sequence and an enhanced mismatch discrimination as compared to the corresponding wild type polymerase or its Klenow fragment, wherein in the modified motif C sequence at least the amino acid residue Q879 has been replaced with a lipophilic amino acid residue. Thus applicant's claims are clearly drawn to "mutant" family A DNA polymerases. Such is supported by applicant's specification at page 10, line 4, in which applicants state "…they also include thermostable DNA polymerases and their mutants."

Thus while applicants submit that the term "family A DNA polymerase" is defined in the present application as referring to DNA polymerizing enzymes that contain the A motif with the sequence DYSQIELR in their active site, applicants claims are drawn to "mutant family A DNA polymerases" for which the structural limitations associated with applicants referred to "family A DNA polymerases" are not necessarily associated with the claimed mutant family A DNA polymerases". Thus it remains that applicants only

structural limitations refer to the mutated amino acid position and not to the remainder of the “mutated family A DNA polymerase”.

Thus the functional features of having DNA polymerase activity, and especially an enhanced mismatch discrimination activity are not associated with any structural features including the motif A with the sequence DYSQIELR in its active site. While the art may describe family A DNA polymerases (Patel *et al.* (J. Mol. Biol. 308:823-837, 2001, "Patel," copy enclosed), applicants claims are not so limited.

Thus there is no disclosure of any particular structure to function/activity relationship in the single disclosed species. The specification also fails to describe additional representative species of these mutant family A DNA polymerases by any identifying structural characteristics or properties other than the activities recited in claims 1, for which no predictability of structure is apparent. While applicants have functionally defined the claims in terms of the result of a motif C modification of a family A DNA polymerase, the claims are not limited structurally in any way, such that since the claims are drawn to a family A DNA polymerase which has been modified, the claims no longer have any structural limitations. Given this lack of species representative of such an unlimited genus of modified DNA polymerases, as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1, 2, 14-27, 33 and 34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a family A DNA polymerase comprising the amino acid sequence of SEQ ID NO:2, in which the amino acid residue at position Q879 has been replaced with a lipophilic amino acid residue, does not reasonably provide enablement for any family A DNA polymerases or its Klenow fragment having a modified motif C sequence and an enhanced mismatch discrimination as compared to a corresponding wild type polymerase, or its Klenow fragment thereof, wherein in the modified motif C sequence at least the amino acid residue Q879 in the wild type motif C sequence QVH in positions 879-881of the E. coli DNA polymerase Klenow fragment shown in SEQ ID NO: 2, has been replaced by a lipophilic amino acid residue. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection was stated in the previous office action as it applied to previous claims 1, 2, 14-27, 33 and 34. In response to this rejection applicants have amended claims 1, 9, 20, 23 and traverse the rejection as it applies to the newly amended claims.

Applicants traverse this rejection on a similar basis as above, in that Applicants submit that first, one of ordinary skill in the art would know how to make (and use) a

family A DNA polymerase based on the knowledge available at the filing of the present application, as discussed above, family A DNA polymerases were well known, and their structure-function relationship was well characterized. Applicants submit that for example, as described in Patel, family A DNA polymerases have 6 conservative regions that form their active sites, and the tertiary structures of several family A DNA polymerases were characterized. In addition, function of individual amino acids was further studied, which shows that very few (10) amino acid residues within the highly conserved motifs A, B and C have a direct role during nucleotide binding and incorporation, and only those residues are important during catalysis and/or for protein folding need to be maintained, while all other residues are mutable. Thus, applicants submit that both the regions of family A DNA polymerases that may be modified without effecting polymerase activities and the great tolerance of this type of polymerase to modification were known in the art.

Applicants additionally submit that the reference cited in the Office Action, Ngo, is insufficient to support the non-enablement rejection, as this reference was published in 1994, 10 years earlier than the priority date of the present application. Thus, it does not describe the state of art at the time of the present application and Ngo states that it is not known whether there exists an efficient algorithm for predicting the structure of a given protein from its amino acid sequence alone. Applicants submit that computer prediction via algorithms is not the only way that the structure of a given protein may be analyzed. As indicated in Patel, high-resolution crystal structures of several prokaryotic DNA polymerases have been determined, and the structure and function relationship of

these enzymes have been characterized by various means, including sequence alignments, crystal structural analysis, and mutagenesis studies.

Second, applicants submit one of ordinary skill in the art would also know how to modify a family A DNA polymerase to increase its mismatch discrimination activity in view of the present application. The present application provides that mismatch discrimination activity of a family A DNA polymerase may be enhanced by replacing Q879 in the motif C sequence QVH with a lipophilic amino acid residue, such as Gly, Ala, Val, Leu and Ile .

Applicant's amendment of the claims and applicants complete argument is acknowledged and has been carefully considered, however, is not found persuasive for the reasons previously stated and for those reasons repeated herein.

It continues that applicants claims are drawn to any family A DNA polymerase or its Klenow fragment having a modified motif C sequence and an enhanced mismatch discrimination as compared to the corresponding wild type polymerase or its Klenow fragment, wherein in the modified motif C sequence at least the amino acid residue Q879 has been replaced with a lipophilic amino acid residue. Thus applicant's claims are clearly drawn to "mutant" family A DNA polymerases. Such is supported by applicant's specification at page 10, line 4, in which applicants state "…they also include thermostable DNA polymerases and their mutants."

It is the extreme breadth of the claimed genus, by virtue of insufficient structural limitations, that render the scope of applicants claims not enabled

While one of ordinary skill in the art would know how to make (and use) a family A DNA polymerase based on the knowledge available at the filing of the present application, as discussed above, the breadth of the claimed mutant family A DNA polymerases is considerably broader. As discussed above those structural limitations associated with a family a DNA polymerase are not necessarily associated with a mutant family A DNA polymerase.

It is this breadth of the claimed mutant DNA polymerases and the lack of guidance associated with “enhanced mismatch discrimination activity" associated with such a broad genus of mutant DNA polymerases that results in the lack of scope of enablement. While applicants argue that those of skill in the art would know of certain associated structures or domains associated with the claimed DNA polymerases, such are not necessarily associated with the claimed mutant DNA polymerases.

While applicants argue that the reference Ngo et al. is not representative of the skill in the art at the time of filing, and that much has been learned since the publishing of the reference Ngo et al., applicants reference to the teachings of Patel et al. while helpful is not sufficient given the extreme breadth of the claimed genus of “mutant" DNA polymerases

Finally while one of skill in the art would know mechanistically how to modify a family A DNA polymerase to increase its mismatch discrimination activity in view of the present application, it remains that the art and application do not provide guidance as to

the specifics of exactly how to modify a family A polymerase to increase its mismatch discrimination activity.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of amino acid modifications of any family A DNA polymerases which has a modified motif C sequence, thus any mutant family A DNA polymerase. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of those polymerases having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The rejection of claims 1, 2, 14, 15, 17-25, 27, 33, 34 are rejected under 35 U.S.C. 102(b) as being anticipated by Minnick et al. (Journal of Biological Chemistry, Vol 274, No. 5, pp 30676, 1999, See IDS) is hereby withdrawn based upon applicants amendment of the claims and applicants arguments presented in the paper of 7/6/2010.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G. Hutson whose telephone number is 571-272-0930. The examiner can normally be reached on M-F, 7:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mondesi Robert can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

rgh
9/10/2010

/Richard G Hutson/
Primary Examiner, Art Unit 1652